USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 15/715,995, filed Sep. 26, 2017, now U.S. Pat. No. 10,016,435, issued Jul. 10, 2018; which is a continuation of U.S. application Ser. No. 14/091,196, filed Nov. 26, 2013, now U.S. Pat. No. 9,801,881, issued Oct. 31, 2017; which is a continuation of U.S. application Ser. No. 13/869,700, filed Apr. 24, 2013; which is a continuation of U.S. application Ser. No. 13/153,317, filed Jun. 3, 2011; which claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed Jun. 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed Jun. 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed Jun. 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed Jun. 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed Dec. 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed Apr. 5, 2011; all of which are herein incorporated by reference in their entirety.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy is named 25922-819-307SEQ.txt and is 812 bytes in size.

BACKGROUND OF THE INVENTION

Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm,* 2000, 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* 2000, 282-288). In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. See, e.g., C. A. Jeffries, et al., (2003), *Journal of Biological Chemistry* 278:26258-26264; N. J. Horwood, et al., (2003), *The Journal of Experimental Medicine* 197: 1603-1611; Iwaki et al. (2005), *Journal of Biological Chemistry* 280(48):40261-40270; Vassilev et al. (1999), *Journal of Biological Chemistry* 274(3): 1646-1656, and Quek et al. (1998), *Current Biology* 8(20):1137-1140.

SUMMARY OF THE INVENTION

Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, the hematological malignancy is CLL. In some embodiments, the treating the hematological malignancy comprises managing the hematological malignancy. In some embodiments, the hematological malignancy is a B-cell malignancy. In some embodiments, the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid. In some embodiments, the mobilized cells are myeloid cells or lymphoid cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises preparing a biomarker profile for a population of cells isolated from the plurality of cells, wherein the biomarker profile indicates the expression of a biomarker, the expression level of a biomarker, mutations in a biomarker, or the presence of a biomarker. In some embodiments, the biomarker is any cytogenetic, cell surface molecular or protein or RNA expression marker. In some embodiments, the biomarker is: ZAP70; t(14,18); β-2 microglobulin; p53 mutational status; ATM mutational status; del(17)p; del(11)q; del(6)q; CD5; CD11c; CD19; CD20; CD22; CD25; CD38; CD103; CD138; secreted, surface or cytoplasmic immunoglobulin expression; V_H mutational status; or a combination thereof. In some embodiments, the method further comprises providing a second cancer treatment regimen based on the biomarker profile. In some embodiments, the method further comprises not administering based on the biomarker profile. In some embodiments, the method further comprises predicting the efficacy of a treatment regimen based on the biomarker profile. In some embodiments, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma